REMARKS

The Office Action of February 27, 2003 has been received and reviewed. Claims 1-11, 24-25, 27 and 28 are currently pending and all claims stand rejected. Claims 1, 5-8, 10, 11, 24, 27 and 28 have been amended and claims 2-4 and 9 have been canceled as set forth herein. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Sequence Listing

Applicants have amended the specification to include a sequence identifier for the peptide sequence on page 8 and have included a substitute sequence listing. Accordingly, the application should be in compliance with the sequence rules.

Priority

The priority document was forward to the Office on May 15, 2003, thus the priority claim should be perfected.

Information Disclosure Statement

The information disclosure statement filed September 25, 2001 was thought to not comply with 37 C.F.R. § 1.98 because it was thought that the applicants did not properly cite the abstracts listed on Form 1449.

Applicants submit herewith a new Information Disclosure Statement correcting the informalities. Since the date of the corrected IDS is the date of the IDS for determining compliance with 37 C.F.R. § 1.97, no fee is being submitted with the corrected IDS. (*See*, M.P.E.P. § 609, page 600-129).

Oath/Declaration

The oath or declaration was thought to be defective since the provisional application is listed under prior foreign applications. A corrected declaration signed by the inventors is submitted herewith.

Specification

The disclosure was objected to for including informalities. Specifically, it was noted that on page 4 reference was made to Table I and that no Table I exists, but rather that a Table 1 is present in the specification. It was further noted that some spelling errors existed in the specification.

Applicants have corrected the spelling errors noted by the Examiner. Withdrawal of the objection to the specification is requested.

Objections to Claims

Claims 10 and 24 were objected to for including informalities. It was noted that the term "and/or" was thought to be grammatically incorrect and that the word "of" was misspelled in claim 10, line 3. Applicants have amended the claims to correct the informalities. Withdrawal of the objections to claims 10 and 24 is requested.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1-3, 6-8, 10-11, 24-25 and 27-28 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Claims 2-3 have been canceled rendering the rejections thereof moot. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, it was thought that the pending claims read on a genus of a recombinant adenovirus having a tropism for primary chondrocytes, wherein the genus is not claimed with a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time of the invention. Although applicants do not agree that the pending claims are not fully supported by the as-filed specification, to expedite prosecution, independent claims 1, 24, 27 and 28 have been amended.

As amended, claims 1, 24, 27 and 28 reflect the Examiner's statement that "[t]he as-filed specification provides sufficient description of recombinant adenovirus based on a 5 serotype having a tropism for primary human chondrocytes, wherein the tropism is provided by at least a tropism determining part of adenoviral fiber protein of adenoviral protein of a B-type adenovirus." (Office Action, page 5). As amended, claims 1, 24, 27 and 28 are directed to a recombinant chimeric adenovirus having at least a part of a fiber protein of a B-type adenovirus, wherein the tropism for primary human chondrocytes is provided by the B-type adenovirus fiber protein. The term "chimeric" indicates that the B-type fiber protein is different than the serotype of the recombinant adenovirus.

As amended, claims 1, 24, 27 and 28 would convey to one skilled in the art that the inventors had possession of the claimed invention. Accordingly, reconsideration and withdrawal of the written description rejections of claims 1, 6-8, 10-11, 24-25 and 27-28 are requested.

Enablement

Claims 1-8, 10-11, 24-25 and 27-28 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement with respect to how to make and use the invention commensurate in scope with the claims. Claims 2-4 have been canceled rendering the rejections thereof moot. At least partially in view of the amendments to the claims, applicants respectfully traverse the rejections.

Specifically, it was thought that the specification is not enabling for a method of delivering a nucleic acid of interest to a primary chondrocyte comprising providing a recombinant adenovirus having a tropism for primary human chondrocytes and for a method of inhibiting cartilage disease progression or repairing cartilage in a human using the claimed recombinant adenovirus, but that the specification enabled delivering a nucleic acid of interest *in vitro* with a recombinant adenovirus based on serotype 5 wherein a tropism for primary human chondrocytes is provided by a tissue determining part of an adenoviral fiber protein of a B-type adenovirus. (*See*, Office Action, page 8). It was also asserted that one would not have known how to make and use the claimed invention so that it would operate as intended. (*See*, *Id.* at page 8). Another basis of the rejections was that the claims did not recite a structural recitation of a

promoter operatively linked to a nucleotide sequence to direct nucleotide expression. Applicants will address the enablement rejections for each independent claim separately for the sake of clarity.

Claim 1

As amended, independent claim 1 is directed to a method "of delivering a nucleic acid of interest to a primary human chondrocyte" with "a recombinant chimeric adenovirus ... comprising a nucleic acid of interest operatively linked to a promoter; a deletion in a gene encoding a fiber protein; a nucleic acid replacing the deletion in the gene of the fiber protein, the nucleic acid encoding at least a part of a fiber protein of a B-type adenovirus; wherein said at least a part of the fiber protein of the B-type adenovirus has a tropism for primary human chondrocytes; and infecting a primary human chondrocyte with said recombinant chimeric adenovirus." Claim 1 is not directed to using the adenovirus in a method of inhibiting cartilage disease progression or repairing cartilage, but is directed to a method of delivering a nucleic acid of interest to a human chondrocyte.

As amended, claim 1 should be considered enabled since, as stated in the Office Action, the as-filed specification "provides sufficient guidance or factual evidence to make and use a recombinant adenovirus based on a 5 serotype having a tropism for primary human chondrocytes, wherein said tropism is provided by at least a tropism determining part of adenovirus fiber protein of a B-type adenovirus." (*Id.* at page 10). As further stated in the Office Action, the specification "provides sufficient guidance for a method of delivering ... a nucleic acid of interest to a primary human chondrocyte." (*Id.* at page 12). Additionally, since the specification discloses examples of recombinant chimeric adenovirus that deliver a gene of interest to chondrocytes, *e.g.*, a recombinant chimeric adenovirus effectively delivers the gene encoding luciferase, lacZ and the gene encoding green fluorescent protein to primary human chondrocytes, claim 1 should be considered enabled. (*See*, Specification, Examples 5-7, paragraph **[0056]-[0059]**).

Accordingly, reconsideration and withdrawal of the enablement rejections of claim 1 and claims 5-8 and 10-11 depending therefrom are requested.

Claim 24

Amended claim 24 is directed to chondrocytes having an additional nucleic acid encoding "at least one amino acid sequence that inhibits cartilage disease progression; at least one amino acid sequence that counteracts the loss of cartilage; or a combination thereof" wherein the additional nucleic acid is provided by a recombinant chimeric adenovirus having a tropism for chondrocytes. Since the as-filed specification discloses that a recombinant chimeric adenovirus having a tropism for chondrocytes is able to successfully transduce chondrocytes with the gene encoding luciferase, lacZ and the gene encoding green fluorescent protein, *e.g.*, Examples 5-7, the specification should also be enabled for chondrocytes provided with the additional nucleic acid as recited in claim 24. (*See, Id.*).

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (M.P.E.P. § 2164.01, *quoting United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). Thus, it would not require undue experimentation to replace the gene encoding luciferase, lacZ or the gene encoding green fluorescent protein in the recombinant chimeric adenovirus having a tropism for primary human chondrocytes in Examples 5-7 of the specification with a nucleic acid sequence encoding the least one amino acid sequence that inhibits cartilage disease progression or that counteracts the loss of cartilage, such as a bone morphogenesis protein.

Reconsideration and withdrawal of the enablement rejections of claim 24 and claim 25 depending therefrom are requested.

Claims 27 and 28

Claims 27 and 28 are directed to a method of inhibiting cartilage disease progression and a method of repairing cartilage, respectively. The Office Action asserted "the specification only provides sufficient guidance for a method of delivering a nucleic acid of interest to a primary human chondrocyte *in vitro*" and that "it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant adenovirus generates a therapeutic effect." (Office Action, pages 10 and 13).

As stated in the MPEP "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example correlates with a disclosed or claimed method invention." (M.P.E.P. § 2164.02). Thus, the examples of the recombinant chimeric adenoviruses in Examples 4-6 of the as-filed specification would allow one of skill in the art to inhibit cartilage disease progression or repair cartilage without undue experimentation since the *in vitro* examples correlate to the claimed methods of claims 27 and 28. For instance, since the examples in the specification teach that the recombinant chimeric adenoviruses having a tropism for primary human chondrocytes and including a nucleic acid of interest operatively linked to a promoter can be delivered to and effectively transduce human chondrocytes *in vitro* (*See*, Specification, paragraphs **[0056]-[0059]**), one of skill in the art would be able to incorporate a nucleic acid encoding a protein useful in inhibiting cartilage disease progression or repairing cartilage, such as a nucleic acid encoding a bone morphogenesis protein, into the recombinant chimeric adenovirus of claim 27 or claim 28 without undue experimentation.

"If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." (M.P.E.P. § 2164.01(c), *citing In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960)). Since the specification includes a connotation of how to use the recombinant adenovirus of claims 27 and 28 and the art recognizes that standard modes of administration are known, the methods of claims 27 and 28 should be considered as enabled.

For instance, the as-filed specification indicates the recombinant chimeric adenovirus can deliver a nucleic acid "to primary human chondrocytes [wherein the nucleic acid] either encodes an amino acid sequence that inhibits cartilage disease progression or a amino acid sequence that counteracts the loss of cartilage. The nucleic acid can encode a member of the family of bone morphogenesis proteins." (Specification, paragraph **[0017]**, page 8). Further, the art recognizes that standard modes are administration are known as exemplified by Arai et al. reference of record that states "[u]sing adenovirus vector, foreign genes can be transduced easily and efficiently into a target tissue," (Arai et al., *infra*, page 1787). As also known in the art, once a recombinant adenovirus or vector is targeted to a specific cell type, pre-clinical studies to

determine the proper amount of vector to use, the rate of administration and the composition or diluent used to administer the vector are within the purview of one of skill in the art and does not require undue experimentation. Accordingly, amended claims 27 and 28 should be considered enabled and reconsideration and withdrawal of the enablement rejections of claims 27 and 28 are requested.

In view of the amendments and remarks presented herein, reconsideration and withdrawal of the enablement rejections of claims 1, 5-8, 10-11, 24-25 and 27-28 are requested.

Rejections under 35 U.S.C. § 102

35 U.S.C. § 102(e)

Claims 1-8 stand rejected under 35 U.S.C. § 102(e) as assertedly being anticipated by Wickham et al. (US Pat. 6,455,314) or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Doherty et al. (Osteoarthritis and Cartilage, Vol. 6, pp. 153-160, 1998). Claims 2-4 have been canceled rendering the rejections thereof moot. Applicants respectfully traverse the rejections as hereinafter set forth.

Wickham et al. does not anticipate amended claim 1 since Wickham et al. does not disclose all of the elements of claim 1. Claim 1 includes a method of delivering a nucleic acid of interest to a primary human chondrocyte comprising providing a recombinant chimeric adenovirus having a nucleic acid encoding at least a part of a fiber protein of a B-type adenovirus. Wickham et al. does not have an enabling disclosure of providing a recombinant chimeric adenovirus having a tropism for primary human chondrocytes, wherein the recombinant chimeric adenovirus includes a nucleic acid encoding a part of a fiber protein of a B-type adenovirus. In fact, none of the Examples in Wickham et al. disclose a recombinant chimeric adenovirus having a fiber protein of a B-type adenovirus or a recombinant chimeric adenovirus having a tropism for primary human chondrocytes. (*See*, Wickham et al., Examples 1-10, Col. 17-24). Further, Wickham et al. does not disclose the infection of a primary human chondrocyte with a recombinant chimeric adenovirus as recited in claim 1.

Accordingly, reconsideration and withdrawal of the anticipation rejections of claim 1 and claims 5-8 depending therefrom are requested.

With regard to the rejections of claim 1-8 under 35 U.S.C. § 103(a) over Doherty et al. asserted in conjunction with the § 102(e) rejection by Wickham et al., the Office Action indicated "Wickham does not specifically teach infecting human chondrocytes, however, Doherty teaches that human chondrocytes were used in adenovirus vector-gene transduction studies." (Office Action, page 15). However, applicants submit that since Wickham et al. does not anticipate claims 1-8, that the 103(a) rejections of claims 1-8 in view of Doherty et al. should also be reconsidered and withdrawn.

35 U.S.C. § 102(b)

Claims 1-8 further stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Doherty et al. Claims 2-4 have been canceled rendering the rejections thereof moot. Applicants respectfully further traverse the rejections as hereinafter set forth.

As amended, claim 1 recites in part "providing a recombinant chimeric adenovirus having a tropism for primary human chondrocytes, said recombinant chimeric adenovirus comprising ... a nucleic acid replacing the deletion in the gene [encoding a fiber protein], said nucleic acid encoding at least a part of a fiber protein of a B-type adenovirus." Doherty et al. does not disclose a recombinant chimeric adenovirus having at least part of a fiber protein of a B-type adenovirus, but is limited to use of AdlacZ which "is an E1 and E3-deleted replication defective adenoviral vector." (Doherty et al., page 154). Thus, claim 1 is not anticipated by Doherty et al.

Accordingly, reconsideration and withdrawal of the anticipation rejections of claim 1 and claims 5-8 depending therefrom are requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 10 and 24

Claims 1, 10 and 24 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Doherty et al. taken with Arai et al. (J. Rheumatol, Vol. 24, pp. 1787-95, 1997). Applicants respectfully traverse the rejections as hereinafter set forth.

A *prima facie* case of obviousness cannot be established with respect to amended independent claim 1 since Doherty et al. and Arai et al. do not, alone or in combination, teach or

suggest each and every element of claim 1. As previously discussed herein, Doherty et al. does not suggest or motivate a recombinant chimeric adenovirus having at least part of a fiber protein of a B-type adenovirus as required by amended claim 1. Further, Arai et al. does not suggest or motivate a recombinant chimeric adenovirus having at least part of a fiber protein of a B-type adenovirus as required by claim 1. (*See*, Arai et al., page 1788, under heading "Materials and Methods, *Adenovirus vector*.")

Since the cited references do not suggest or motivate all of the elements of independent claim 1, a *prima facie* case of obviousness cannot be established. Claim 10 is not obvious, at the very least, as depending from non-obvious independent claim 1. (*See, In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

A *prima facie* case of obviousness also cannot be established with regard to independent claim 24 since the cited references do not, alone or in combination, teach or suggest all the elements of claim 24. Claim 24 is directed to chondrocytes provided with an additional nucleic acid, wherein the additional nucleic acid is provided by a recombinant chimeric adenovirus having a nucleic acid encoding at least a part of a fiber protein of a B-type adenovirus. As previously discussed herein, Doherty et al. and Arai et al. do not, alone or in combination, suggest or motivate a recombinant chimeric adenovirus having at least part of a fiber protein of a B-type adenovirus as required to establish obviousness.

Reconsideration and withdrawal of the obviousness rejections of claim 24 are, thus, requested.

Claims 1, 11 and 24-25

Claims 1, 11 and 24-25 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Doherty et al. taken with Arai et al. in further view of either Duprez et al. (IDS, Mechanism of Development, Vol. 57, abstract, 1996) or Noh et al. (US Pat. 6,315,992). Applicants respectfully traverse the rejections as hereinafter set forth.

The Office Action indicated that the "rejection of the base claims 1 and 24 under 103(a) is applied as indicated above." (Office Action, page 18). Thus, since a *prima facie* case of obviousness cannot be established with regard to claims 1 and 24 as previously established

herein, dependent claims 11 and 25 are not obvious, at the very least, as depending from nonobvious independent claims 1 and 24, respectively. (*See*, *In re Fine*, *supra*).

Accordingly, reconsideration and withdrawal of the obviousness rejections of claims 1, 11 and 24-25 are respectfully requested.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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